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Dated: March 22, 2005 Signature: John Murray
(John Murray, Ph.D.)

Docket No.: 8642/91
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Gary J. NABEL *et al.*

Application No.: 09/663,889 Confirmation No.: 6450

Filed: September 18, 2000 Art Unit: 1632

For: KITS FOR SITE-SPECIFICALLY TRANSFORMING CELLS *IN VIVO* Examiner: Kelly, Robert M.

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Appeal Brief is provided in support of Appellants' appeal from the Final Rejection dated August 26, 2004, in the above-identified case, in which claims 17 and 19-36, i.e., all pending claims, were finally rejected.

(1) REAL PARTY IN INTEREST

The present application is owned by The Regents of the University of Michigan and exclusively licensed to Boston Scientific Corporation.

(2) RELATED APPEALS AND INTERFERENCES

There are no known appeals or interferences that will directly affect or be directly affected by or have a bearing on this appeal.

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(3) STATUS OF CLAIMS

Claims 17 and 19-36 are as set forth in Appellants' Amendment and Request for Reconsideration under 37 C.F.R. 1.116 filed concurrently with the Appeal Brief. The rejection of all claims is hereby appealed.

(4) STATUS OF AMENDMENTS

An after final amendment, entitled "An Amendment and Request for Reconsideration under 37 C.F.R. 1.116" is filed concurrently with this Appeal Brief. Claims 21, 35 and 36 are amended to correct clerical errors.

(5) SUMMARY OF INVENTION

The present invention relates to a combination for site-specifically transforming cells *in vivo*, which combination comprises a catheter and a nucleic acid. The nucleic acid comprises a gene encoding p21, as set forth in independent claim 17. The catheter may be, for example, a double balloon catheter (claim 19). Page 19, lines 3 to 6 of the Appellants' specification describes the claimed combination: A double balloon catheter comprising an adenovirus-p21 expression vector introduced into the iliofemoral arteries of domestic pigs for the purpose of transforming the cells of the arteries. Methods of preparing a nucleic acid encoding p21 are described in the specification at page 6, lines 14 to 24.

The combination may further comprise a pharmaceutical carrier (claim 20) and the pharmaceutical carrier may comprise the nucleic acid (claim 21). The pharmaceutical carrier may be any suitable carrier that facilitates delivery and/or expression of the nucleic acid. Examples of such pharmaceutical carriers are described in the specification at, for example, page 9, lines 13 to 23.

The nucleic acid may be an expression vector (claim 22) and the expression vector may comprise a viral promoter (claim 23), e.g., a Cytomegalovirus ("CMV") promoter (claim 24) or Respiratory Syncytial Virus ("RSV") promoter (claim 25). Expression vectors containing a nucleic acid encoding p21 are described in the specification at, for example, page 5, line 22 to page 6, line 23. Various promoters are described in the specification at page 5, lines 16-21.

A viral particle may comprise the nucleic acid (claim 26) and the viral particle may be, for example, an adenoviral particle (claim 27) or a retroviral particle (claim 28). Viral particles are described in the specification on, for example, page 5, line 22 to page 6, line 1. Adenoviral and retroviral particles are particularly recited on page 6, lines 1 to 13.

The combination described in claim 17 may further comprise a liposome, as set forth in claim 29, and the liposome may comprise the nucleic acid (claim 30). A liposome delivery system is described in the specification at page 7, lines 8 to 16 and at page 8, lines 9 to 26.

The nucleic acid of the combination of claim 17 may further comprise a second gene (claim 31). The second gene preferably encodes HLA-B7, an immunotherapeutic agent, a cytokine, or a prodrug-converting enzyme (claim 32). The prodrug-converting enzyme may be thymidine kinase (claim 33). The specification describes the possible second genes on page 11, line 19 to page, 12 line 2.

The gene encoding p21 and the second gene may be operatively linked (claim 34); and the gene encoding p21 and the second gene may be linked such that they encode a fusion protein (claim 35). An example of such fusion protein is a p21-thymidine kinase fusion protein (claim 36). Such embodiments are described in the specification at page 7, line 17 to page 8, line 8.

(6) ISSUES

Whether Claims 17 and 19-36 comply with the written description requirement of 35 U.S.C. §112, first paragraph.

Whether Claims 17 and 19-36 are novel and not anticipated under 35 U.S.C. §102(b) by Nabel et al. (U.S. Patent 5,863,904).

Whether Claims 17, 20-22 and 31 are novel and not anticipated under 35 U.S.C. §102(b) by Xiong et al. 366 Nature 701 (1993).

Whether Claims 17 and 19 are patentable under 35 U.S.C. 103(a) over Xiong in view of Nabel 249 Science1285 (1990).

Whether the Examiner has committed an error in denying Applicants' claim to priority of the parent applications for purportedly failing to fulfill the requirements of 35 U.S.C. 120 by

purportedly not meeting the requirements of the first paragraph of 35 U.S.C. 112, written description and new matter. Whether the Examiner has committed an error in alleging a supplemental oath is required because the claims allegedly contain new matter.

(7) ARGUMENTS

(i) Claims 17 And 19-36 Comply With The Written Description Requirement Under 35 U.S.C. §112, First Paragraph.

1. The Specification Describes A Combination Of A Catheter And A Nucleic Acid Comprising A Gene Encoding P21.

Claims 17 and 19-36 stand rejected under 35 U.S.C. §112, first paragraph for purportedly failing to comply with the written description requirement. The Examiner contends that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one of skill in the relevant art that at the time the application was filed the inventors had possession of the claimed invention. In particular, the Examiner contends that the specification does not support the combination set forth in pending claim 17 of a catheter and a nucleic acid comprising a gene encoding p21, as noted in the following Office Action quotation:

> The specification provides no implicit or explicit support for a combination comprising a catheter and a nucleic acid comprising a gene encoding p21 ....The specification has only provided for the use of a catheter and an expression vector ... in a treatment, but has not otherwise even contemplated a combination, as a product comprising the same. (Office Action dated January 29, 2004, page 6, first paragraph). Moreover, the Artisan would not have understood that the Applicant was in possession of the claimed combination at the time of invention because the Artisan would not have understood a combination to be a product of a catheter comprising a solution of a nucleic acid encoding p21 ....
>
> (Office Action August 25, 2004 paragraph spanning page 5-6)

The Examiner also contends that the claims relating to a "combination comprising a nucleic acid comprising a p21 gene and a catheter are not described in the instant application and therefore constitute new matter" (Office Action dated August 25, 2004, page 7, 2nd paragraph.) The Examiner's position is erroneous.

The written description requirement of Section 112 requires only that the application convey to one of skill in the art that they invented what is now claimed. *In re Edwards*, 568 F.2d 1349, 1352, 196 USPQ 465, 467 (C.C.P.A. 1978). Furthermore, the written description requirement does not require the applicant "to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now claimed." *Union Oil Co. of Cal v Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000). The following passages demonstrate that Appellants' specification describes a combination of a catheter and a nucleic acid molecule encoding p21 for site-specifically transforming cells *in vivo*:

> Direct gene transfer was performed in the iliofemoral arteries of Yorkshire pigs using a double balloon catheter as described (Nabel et al. 1990, Science 249:1285-1288). In each animal, both iliofemoral arteries were infected with the same vector at a titer of 1×10^{10} pfu/ml, and 0.7 ml was used in each animal (final dose of 7×10^{9} pfu) (Ohno et al., 1994, Science 265:781-784: Chang et al. 1995 Science 267:518-522)
>
> (Specification page 14, lines 18-24; the '904 Patent Col. 6, lines 51-58);

and

> To assess the direct effect of p21 on vascular cell growth *in vivo*, p21 vectors were introduced into porcine arteries immediately following injury. The right and left iliofemoral arteries of domestic pigs were balloon injured and infected with ADV-p21 or ADV-Δ. El using a double-balloon catheter (1×10^{10} pfu/ml, 0.7×10^{10} pfu total dose). In vivo gene transfer of ADV-p21 was demonstrated in injured porcine arteries 7 days after infection ....
>
> (Specification page 19, lines 3-8; the '904 Patent Col. 8, lines 36-40);

and

> These results suggest that infection of arteries with ADV-p21 at the time of balloon injury inhibits the proliferation of intimal smooth muscle cells and significantly limits the development of a neointima.
>
> (Specification page 19, line 22 to page 20 line 2; the '904 Patent Col. 8, lines 57-60).

The vector referenced in these passages is ADV-p21, a p21-encoding adenoviral vector. The foregoing passages (which are also recited in the parent applications serial no. 08/533,942, which matured into US Patent 5,863,904 ("the '904 Patent"), serial no. 09/031,572, which matured into U.S. Patent No. 6,057,300 and serial no. 09/426,325, which matured into U.S. Patent 6,218,372) describe the combination of a catheter and a nucleic acid molecule encoding p21, as recited in the claims. In addition, Appellants reduced the claimed invention to actual practice by using a catheter, more particularly a double balloon catheter, to successfully transfer a p21-encoding vector to cells of both iliofemoral arteries (Specification page 12, Example 1). Moreover, the term "combination" would naturally occur to one skilled in the art reading the description of the catheter with a p21 encoding nucleic acid for site-specifically transforming cells *in vivo*. The specification clearly conveys to one skilled in the art that the catheter in combination with a p21-encoding nucleic acid are necessarily materials used by which Appellants' site-specific transformation method works, as described in this application.

As in *In re Smythe and Shamos*, this is not a case where there is any unpredictability such that Appellants' description of a catheter in combination with p21-encoding nucleic acid would not convey to one skilled in the art that Appellants invented a combination of a catheter and a p21-encoding nucleic acid to site-specifically transform cells *in vivo*. See *In re Smythe and Shamos,* 480 F.2d 1376, 1384, 178 USPQ 279, 285 (C.C.P.A. 1973)(holding that a description of the use and function of a segmentizing medium conveyed to one skilled in the sample-analysis art the knowledge that applicants invented a sample analyzer with an inert fluid segmentizing medium.) Based on Appellants' description of the site-specific transformation of cells *in vivo* with a catheter and a nucleic acid encoding p21, one of skill in the art would have understood that Appellants were in possession of the combination of a catheter and a nucleic acid comprising a gene encoding p21 for site-specifically transforming cells *in vivo* as described in the claims.

While the specification does not explicitly recite the term "combination", it is unnecessary for the application to describe the claimed subject matter in exactly the same terms as used in the claims. *Union Oil Co. of Cal.,* 208 F.3d at 997, 54 USPQ2d at 1232(holding that verbatim correspondence between claim language and specification is not necessary to satisfy the written description requirement of section 112). Instead, the disclosure need only reasonably

convey to persons skilled in the art that the inventor had possession of the subject matter in question. *In re Edwards*, 568 F.2d at 1352, 196 U.S.P.Q. at 467. As discussed *supra*, Appellants have provided sufficient description of the claimed combination that one of skill in the art upon reading Appellants' specification would comprehend that Appellants had invented a combination of a catheter and nucleic acid encoding p21 to site specifically transform cells *in vivo*.

The foregoing demonstrates that the application provides sufficient written description of the invention as claimed to satisfy the requirements of 35 U.S.C. 112.

(ii) Claims 17 and 19-36 Are Novel Under 35 U.S.C. §102(b) In View Of Nabel et al. (the '904 patent)

Claims 17 and 19-36 stand rejected under 35 U.S.C. §102(b) for purportedly being anticipated by the '904 Patent, which was filed September 26, 1995. Under 35 U.S.C. 102(b), a person shall be entitled to a patent unless "the invention was patented ... more than one year prior to the date of the application for patent in the United States." As discussed above, Appellants' invention as now claimed is supported fully by both the present application and the parent applications.[1] As such, the claims are entitled to the priority date of the first filed parent application, serial number 08/533,942, which matured into the '904 Patent, and that priority date was September 26, 1995. Thus the '904 Patent is not prior art and cannot support a rejection of the claims under 35 U.S.C. 102(b).

In view of the foregoing, the rejection of the claims under 35 U.S.C. §102(b) over the '904 Patent is erroneous and should be withdrawn.

(iii) Claims 17, 20-22 and 31 Are Novel Under 35 U.S.C. §102(b) in view of Xiong et al. (366 Nature 701 (1993)

Claims 17, 20-22 and 31 stand rejected under 35 U.S.C. 102(b) for purportedly being anticipated by Xiong et al., 366 Nature 701 (1993) ("Xiong"). Anticipation under 35 U.S.C. §102 requires the disclosure in a single piece of prior art of each and every element of a claimed invention. *Electro Med. Sys. S.A. v. Cooper Life Sciences,* 34 F.3d 1048, 1052, 32 USPQ2d 1017, 1019 (Fed. Cir. 1994). The claim element "catheter," given its broadest reasonable

[1] Appellants note that by rejecting their priority claim and at the same time applying the subject of this claim, i.e. the '904 patent, which matured from serial number 08/533,942, as a 35 U.S.C. §102(b) reference against the claims, the Examiner is taking an inconsistent position.

interpretation, and a combination of a catheter and a nucleic acid comprising a gene encoding p21, are not disclosed by Xiong. Accordingly, Xiong can not anticipate the invention as claimed.

The Examiner, for the purpose of this rejection, has interpreted the term "catheter" broadly such that "it reads on tubing, such as a pipette tip or an Eppendorf tube." The Examiner concludes that wherever "p21 cDNA was present in tubing such as a pipette tip or an Eppendorf tube the claims were anticipated." (Office Action January 29, 2004 at page 9.) It is well accepted that the PTO may give claim language the broadest reasonable interpretation consistent with the specification and claim language should be read in light of the specification as it would by one of ordinary skill in the art. *See In Re Smeed,* 710 F.2d 1544, 1548, 218 USPQ 385, 388 (Fed. Cir. 1983). The Examiner's reading of the term "catheter" to encompass pipette tips and Eppendorf tubes is improperly overbroad because it expands the meaning of the term beyond that which was intended by the inventor as set forth in the specification.

The term catheter has a well defined meaning to those of skill in the art. The American Heritage Dictionary of the English Language (American Heritage Publishing Col, Inc. 1970 at p. 213) defines a catheter as a "slender, flexible tube of metal, rubber, or plastic inserted into a body channel, such as a vein, to distend or maintain an opening to an internal cavity." Such a definition does not encompass either a pipette tip or an Eppendorf tube. Nor would one of skill in the art understand that the catheter described in Appellants' Examples would encompass a pipette tip or an Eppendorf tube. Accordingly, the term "catheter" as recited in the claims does not encompass either a pipette tip or an Eppendorf tube.

For a reference to support a rejection under Section 102(b), it must disclose each and every limitation of the claims. *Electro Med. Sys. S.A., supra.* Xiong fails to disclose a catheter or a combination of a catheter and a nucleic acid molecule comprising a gene encoding p21. Thus Xiong fails to disclose each and every element of the claims and as such does not anticipate the claimed subject matter. The rejection of the claims under 35 U.S.C. § 102(b) over Xiong is erroneous and should be withdrawn.

(iv) Claims 17 And 19 Are Unobvious Under 35 U.S.C. 103 In View Of Xiong et al. (366 Nature 701 (1993) And Nabel et al. (249 Science 1285 (1990)

Claims 17 and 19 stand rejected for purportedly being unpatentable over the combination of Xiong et al. (366 Nature 701 (1993) ("Xiong") and Nabel et al. (249 Science 11285 (1990) (Nabel). The Examiner contends Xiong teaches the cloning of cDNA encoding p21 and discloses that p21 inhibits cell proliferation upon overexpression in mammalian cells. The Examiner acknowledges that Xiong does not teach a double balloon catheter. The Examiner contends Nabel teaches the use of a double-balloon catheter to deliver nucleic acid molecules directly into arterial walls. The Examiner concludes

> one of ordinary skill in the art would have been sufficiently motivated to combine a p21 gene and a catheter as Xiong et al. taught that p21 is an inhibitor of cell proliferation and more particularly because Nabel et al. represent that a double-balloon catheter can be used to introduce recombinant genes, which inhibit smooth muscle cell proliferation, directly in the site of angioplasty to inhibit smooth muscle cell proliferation to prevent restenosis...
>
> (Office Action January 29, 2004, page 11).

The Examiner's conclusion is erroneous. For cited references to support a rejection under 35 U.S.C. 103 there must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination. That knowledge can not come from the applicant's own disclosure. *In re Oetiker*, 977 F.2d 1443, 1447, 24 USPQ2d 1443, 1446 (Fed. Circ. 1992). Although couched in terms of combining teachings found in the prior art, the same inquiry must be carried out in the context of a purportedly obvious "modification" of the prior art. The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification. *In re Fritch*, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992). The following remarks make clear that one of skill in the art would not be motivated to combine Xiong with Nabel in the manner suggested by the Examiner to obtain the claimed invention.

Xiong only teaches that p21 overexpression inhibits *in vitro* proliferation of an established osteosarcoma cell line. Xiong does not teach that p21 has any effect on any other cell type *in vitro* and Xiong provides no information as to the effect of p21 expression at any level *in vivo*. Xiong does not teach that p21 expression has an antithrombotic effect and does not

teach that p21 expression inhibits smooth muscle cell proliferation *in vivo*. Nabel teaches using a catheter to deliver a recombinant gene with antithrombotic effect or gene that inhibits smooth muscle cell proliferation to the site of angioplasty to prevent restenosis. See Nabel at 1287, second column, last paragraph.

But, Nabel fails to teach or suggest which particular recombinant genes exert an antithrombotic effect or inhibit smooth muscle cell proliferation *in vivo*. This information is also absent in Xiong. P21 was not known in the art as "a recombinant gene that exerts an antithrombotic effect or inhibits smooth muscle cell proliferation" and therefore one of skill in the art would not have been motivated to combine a p21-encoding nucleic acid molecule as taught by Xiong with the catheter disclosed in Nabel.

While a nucleic acid comprising a p21-encoding gene could be combined with a catheter to transform cells *in vivo*, this is not the standard for determining obviousness. The question is whether one of skill in the art would make the combination and the foregoing demonstrates that without the instruction provided by applicants' own disclosure one of skill in the art would not be motivated to combine a p21-encoding nucleic acid as taught by Xiong with a catheter in the methods of Nabel. Without this teaching, found in Appellants' disclosure, as a guide, and not finding either suggestion or motivation in Xiong and Nabel for combining them, the rejection under 35 U.S.C. 103 over Xiong in view of Nabel is inappropriate and should be withdrawn.

(v) Appellants' Claims Do Not Contain New Matter And Are Entitled To The Priority Date Of The Parent Applications

The Examiner has denied Appellants' claim to priority to U.S. Serial Nos. 08/533,942, 09/031,572 and 09/462,325 (the parent applications) filed Sep. 26, 1995, February 26, 1998 and October 25, 1999 respectively. The Examiner contends that the present application adds and claims additional disclosure not presented in the prior application and that the claim limitations relating to "a combination which comprises a catheter and nucleic acid comprising a gene encoding p21" are not described in the instant application. In particular, the Examiner states:

> The recited passages describe a method of using a catheter for administration of a vector comprising a p21 gene. However, the recited passages do not describe or suggest a combination of a gene encoding p21 and a catheter as a product. (Office Action January 29, 2004, page 3 lines 16-18)

The Examiner contends that applicants are trying to satisfy the written description through obviousness and cites *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1567, 43 USPQ2d 1398 1405 (Fed. Cir. 1997) ("Lilly") citing *Lockwood v. American Airlines Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997) to support his position.

The Examiner is wrong. Applicant has argued that the specification shows unequivocally that the claimed invention, i.e., the combination of a catheter and a nucleic acid encoding P21, is expressly shown in the patent. As discussed above, the examples of applicants' specification use the combination of a catheter and a nucleic acid encoding P21. Thus, applicants are not arguing such a combination is obvious. Rather, applicants are arguing the specification expressly describes the claimed subject matter.

Furthermore, *Lilly* is not an appropriate cite. In that case, the claims were to a nucleotide sequence and Lilly's application did not describe the claimed sequence. In contrast, the present application expressly describes the combination of a catheter and a nucleic acid encoding P21 for which Appellants seek claims.

The foregoing remarks demonstrate that Appellants' claims are not only supported by the written description in the present application but are also supported by the parent applications. As such, the combination for site-specifically transforming cells *in vivo* that comprises a catheter and a p21 encoding nucleic acid, as now claimed, is not new matter and is entitled to the priority of the parent applications.

(vi) A New Oath/Declaration Is Unnecessary

The Examiner contends that the claims are not originally claimed or embraced in the statement of invention and therefore a new oath is required. Appellants submit that a new oath or declaration is not required.

Claims in a continuation application directed to originally disclosed subject matter that was not claimed as part of the invention of a parent application are entitled to the benefit of the filing date of the parent application. *In re Brower,* 433 F.2d 813, 817, 167 USPQ 684, 687 (C.C.P.A. 1970). As discussed *supra*, the appealed claims are fully supported by the parent applications and as such the claims do not contain new matter. Appellants are entitled to claim properly supported subject matter at any time during the pendency of the application.

Accordingly, the original oath encompasses the disclosed and presently claimed invention and as such a new oath/declaration in this application is unnecessary.

CONCLUSION

The pending claims describe a combination of a catheter and a p21-encoding nucleic acid molecule that is described in the present application and the parent priority applications. The present and parent priority applications provide a clear description of a method that uses a combination of a catheter and a p21-encoding nucleic acid molecule. Support for the pending claims is therefore also present in the current specification. The aforementioned method has been claimed in the issued '904 Patent. Accordingly, Appellants submit that the Examiner's denial of priority and rejection of claims 17 and 19-36 under 35 U.S.C. § 112, first paragraph should be reversed.

Applying the '904 Patent under 35 U.S.C. § 102(b) is inappropriate in view of Appellants' proper priority claim. The remaining cited references do not teach or suggest the claimed subject matter. In particular, Xiong does not disclose every element of the claims and therefore cannot anticipate the claimed subject matter under 35 U.S.C. § 102(b). One of skill in the art would not be motivated to combine Xiong and Nabel in the manner suggested by the Examiner and do not render claims 17 and 19 obvious under 35 U.S.C. 103(a). Accordingly, Appellants submit that claims 17 and 19-36 are fully patentable over the cited references, and the Examiner's rejections should be reversed.

(8) APPENDIX

The attached appendix includes the claims under appeal.

Dated: March 22, 2005

Respectfully submitted,

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APPENDIX

17 A combination for site-specifically transforming cells *in vivo* comprising a catheter and a nucleic acid comprising a gene encoding p21.

19 The combination of claim 17, wherein the catheter is a double balloon catheter.

20 The combination of claim 17, further comprising a pharmaceutical carrier.

21 The combination of claim 20, wherein the pharmaceutical carrier comprises the nucleic acid.

22 The combination of claim 17, wherein the nucleic acid is an expression vector.

23 The combination of claim 22, wherein the expression vector comprises a viral promoter.

24 The combination of claim 23, wherein the viral promoter is a CMV promoter.

25 The combination of claim 23, wherein the viral promoter is a RSV promoter.

26 The combination of claim 17, wherein a viral particle comprises the nucleic acid.

27 The combination of claim 26, wherein the viral particle is an adenovirus particle.

28 The combination of claim 26, wherein the viral particle is a retrovirus particle.

29 The combination of claim 17, further comprising a liposome.

30 The combination of claim 29, wherein the liposome comprises the nucleic acid.

31 The combination of claim 17, wherein the nucleic acid comprises a second gene.

32 The combination of claim 31, wherein the second gene encodes HLA-B7, an immunotherapeutic agent, cytokine, or prodrug converting enzyme.

33 The combination of claim 32, wherein the prodrug converting enzyme is thymidine kinase.

34 The combination of claim 31, wherein the gene encoding p21 and the second gene are operatively linked.

35 The combination of claim 34, wherein the gene encoding p21 and the second gene are operatively linked such that they encode a fusion protein.

36 The combination of claim 35, wherein the fusion protein is a p21-thymidine kinase fusion protein.